

We Claim:

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- 5 1. An isolated nucleic acid molecule selected from the group consisting of:
- a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:3 or a complement thereof;
 - b) a nucleic acid molecule comprising a fragment of at least 100 contiguous nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:3 or a complement thereof;
 - c) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:4;
 - d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the fragment comprises at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:4;
 - e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:3 under stringent conditions; and
 - f) a nucleic acid molecule which is antisense to the coding strand of a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:3.
- 10 2. The nucleic acid molecule of claim 1 further comprising vector nucleic acid sequences.
- 15 3. The nucleic acid molecule of claim 1 further comprising nucleic acid sequences encoding a heterologous polypeptide.
- 20 4. A host cell which contains the nucleic acid molecule of claim 1.
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- 30 5. An isolated nucleic acid molecule selected from the group consisting of:
- a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:5 or a complement thereof;
 - b) a nucleic acid molecule comprising a fragment of at least 100 contiguous nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:5 or a complement thereof;
 - c) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:6;
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d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:6, wherein the fragment comprises at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:6;

e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:6, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:5 under stringent conditions; and

f) a nucleic acid molecule which is antisense to the coding strand of a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:5.

6. The nucleic acid molecule of claim 5 further comprising vector nucleic acid sequences.

7. The nucleic acid molecule of claim 5 further comprising nucleic acid sequences encoding a heterologous polypeptide.

8. A host cell which contains the nucleic acid molecule of claim 5.

9. An isolated polypeptide selected from the group consisting of:

a) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:4;

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:3 under stringent conditions;

c) a polypeptide which is encoded by the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:3; and

d) a polypeptide comprising the amino acid sequence of SEQ ID NO:4.

10. The fusion protein comprising the polypeptide of claim 9 operatively
35 linked to heterologous amino acid sequences.

11. /An antibody which selectively binds to a polypeptide of claim 9.

12. A method for producing a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:4;

b) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:4; and

c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:3 under stringent conditions;

comprising culturing the host cell of claim 4 under conditions in which the
15 nucleic acid molecule is expressed.

13. An isolated polypeptide selected from the group consisting of:

a) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:6, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:6;

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:6, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:5 under stringent conditions;

c) a polypeptide which is encoded by the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:5; and

d) a polypeptide comprising the amino acid sequence of SEQ ID NO:6.

14. The fusion protein comprising the polypeptide of claim 13 operatively linked to heterologous amino acid sequences.

15. An ~~antibody~~ which selectively binds to a polypeptide of claim 13.

| | 1970 | 1971 | 1972 | 1973 | 1974 | 1975 | 1976 | 1977 | 1978 | 1979 | 1980 | 1981 | 1982 | 1983 | 1984 | 1985 | 1986 | 1987 | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 | 2032 | 2033 | 2034 | 2035 | 2036 | 2037 | 2038 | 2039 | 2040 | 2041 | 2042 | 2043 | 2044 | 2045 | 2046 | 2047 | 2048 | 2049 | 2050 | 2051 | 2052 | 2053 | 2054 | 2055 | 2056 | 2057 | 2058 | 2059 | 2060 | 2061 | 2062 | 2063 | 2064 | 2065 | 2066 | 2067 | 2068 | 2069 | 2070 | 2071 | 2072 | 2073 | 2074 | 2075 | 2076 | 2077 | 2078 | 2079 | 2080 | 2081 | 2082 | 2083 | 2084 | 2085 | 2086 | 2087 | 2088 | 2089 | 2090 | 2091 | 2092 | 2093 | 2094 | 2095 | 2096 | 2097 | 2098 | 2099 | 2100 | 2101 | 2102 | 2103 | 2104 | 2105 | 2106 | 2107 | 2108 | 2109 | 2110 | 2111 | 2112 | 2113 | 2114 | 2115 | 2116 | 2117 | 2118 | 2119 | 2120 | 2121 | 2122 | 2123 | 2124 | 2125 | 2126 | 2127 | 2128 | 2129 | 2130 | 2131 | 2132 | 2133 | 2134 | 2135 | 2136 | 2137 | 2138 | 2139 | 2140 | 2141 | 2142 | 2143 | 2144 | 2145 | 2146 | 2147 | 2148 | 2149 | 2150 | 2151 | 2152 | 2153 | 2154 | 2155 | 2156 | 2157 | 2158 | 2159 | 2160 | 2161 | 2162 | 2163 | 2164 | 2165 | 2166 | 2167 | 2168 | 2169 | 2170 | 2171 | 2172 | 2173 | 2174 | 2175 | 2176 | 2177 | 2178 | 2179 | 2180 | 2181 | 2182 | 2183 | 2184 | 2185 | 2186 | 2187 | 2188 | 2189 | 2190 | 2191 | 2192 | 2193 | 2194 | 2195 | 2196 | 2197 | 2198 | 2199 | 2200 | 2201 | 2202 | 2203 | 2204 | 2205 | 2206 | 2207 | 2208 | 2209 | 2210 | 2211 | 2212 | 2213 | 2214 | 2215 | 2216 | 2217 | 2218 | 2219 | 2220 | 2221 | 2222 | 2223 | 2224 | 2225 | 2226 | 2227 | 2228 | 2229 | 2230 | 2231 | 2232 | 2233 | 2234 | 2235 | 2236 | 2237 | 2238 | 2239 | 2240 | 2241 | 2242 | 2243 | 2244 | 2245 | 2246 | 2247 | 2248 | 2249 | 2250 | 2251 | 2252 | 2253 | 2254 | 2255 | 2256 | 2257 | 2258 | 2259 | 2260 | 2261 | 2262 | 2263 | 2264 | 2265 | 2266 | 2267 | 2268 | 2269 | 2270 | 2271 | 2272 | 2273 | 2274 | 2275 | 2276 | 2277 | 2278 | 2279 | 2280 | 2281 | 2282 | 2283 | 2284 | 2285 | 2286 | 2287 | 2288 | 2289 | 2290 | 2291 | 2292 | 2293 | 2294 | 2295 | 2296 | 2297 | 2298 | 2299 | 2300 | 2301 | 2302 | 2303 | 2304 | 2305 | 2306 | 2307 | 2308 | 2309 | 2310 | 2311 | 2312 | 2313 | 2314 | 2315 | 2316 | 2317 | 2318 | 2319 | 2320 | 2321 | 2322 | 2323 | 2324 | 2325 | 2326 | 2327 | 2328 | 2329 | 2330 | 2331 | 2332 | 2333 | 2334 | 2335 | 2336 | 2337 | 2338 | 2339 | 2340 | 2341 | 2342 | 2343 | 2344 | 2345 | 2346 | 2347 | 2348 | 2349 | 2350 | 2351 | 2352 | 2353 | 2354 | 2355 | 2356 | 2357 | 2358 | 2359 | 2360 | 2361 | 2362 | 2363 | 2364 | 2365 | 2366 | 2367 | 2368 | 2369 | 2370 | 2371 | 2372 | 2373 | 2374 | 2375 | 2376 | 2377 | 2378 | 2379 | 2380 | 2381 | 2382 | 2383 | 2384 | 2385 | 2386 | 2387 | 2388 | 2389 | 2390 | 2391 | 2392 | 2393 | 2394 | 2395 | 2396 | 2397 | 2398 | 2399 | 2400 | 2401 | 2402 | 2403 | 2404 | 2405 | 2406 | 2407 | 2408 | 2409 | 2410 | 2411 | 2412 | 2413 | 2414 | 2415 | 2416 | 2417 | 2418 | 2419 | 2420 | 2421 | 2422 | 2 |
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16. A method for producing a polypeptide selected from the group consisting of:

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- a) a polypeptide comprising the amino acid sequence of SEQ ID NO:6;
 - b) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:6, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:6; and
 - c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:6, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:5 under stringent conditions;
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comprising culturing the host cell of claim 8 under conditions in which the nucleic acid molecule is expressed.

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17. A method for detecting the presence of a MEKK1 polypeptide in a sample comprising:

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- a) contacting the sample with a compound which selectively binds to the polypeptide; and
 - b) determining whether the compound binds to the polypeptide in the sample to thereby detect the presence of a MEKK1 polypeptide in the sample.

18. A kit comprising a compound which selectively binds to a MEKK1 polypeptide and instructions for use.

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19. A method for detecting the presence of a MEKK1 nucleic acid molecule in a sample comprising:

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- a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule; and
 - b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample to thereby detect the presence of a MEKK1 nucleic acid molecule in the sample.

20. A kit comprising a compound which selectively hybridizes to a MEKK1 nucleic acid molecule and instructions for use.

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21. A method for detecting the presence of a biological activity of a MEKK1 polypeptide in a sample comprising:

a) contacting the sample with an agent capable of detecting MEKK1 activity; and

5 b) determining the presence of MEKK1 activity in the sample.

22. A method for modulating MEKK1 activity comprising contacting a cell with an agent that modulates MEKK1 activity such that MEKK1 activity in the cell is modulated.

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23. The method of claim 22 wherein the agent is selected from the group consisting of an antibody that specifically binds to the MEKK1 protein and a nucleic acid molecule having a nucleotide sequence which is antisense to the coding strand of a MEKK1 mRNA of MEKK1 gene.

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24. A method to treat a subject having a disorder characterized by aberrant MEKK1 protein or nucleic acid expression or activity comprising administering an agent which is a MEKK1 modulator to the subject such that MEKK1 protein or nucleic acid expression or activity is modulated.

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25. A method for identifying the presence or absence of a genetic alteration characterized by at least one of (i) aberrant modification or mutation of a gene encoding a MEKK1 protein; (ii) mis-regulation of said gene; and (iii) aberrant post-translational modification of a MEKK1 protein, wherein a wild-type form of said gene encodes an protein with a MEKK1 activity

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26. An isolated active fragment of an MEKK1 protein consisting of an amino acid sequence having at least 75% homology to an amino acid sequence consisting of about amino acids 875-1493 of SEQ ID NO:4, wherein said active fragment mediates apoptosis.

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27. The active fragment of claim 26, which consists of an amino acid sequence having at least 85% homology to an amino acid sequence consisting of about amino acids 875-1493 of SEQ ID NO:4.

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28. The active fragment of claim 26, which consists of an amino acid sequence having at least 95% homology to an amino acid sequence consisting of about amino acids 875-1493 of Figure 9.

5 29. The active fragment of claim 26, which is a mouse MEKK1 active fragment.

30. The active fragment of claim 26, which is a human MEKK1 active fragment.

10 31. The active fragment of claim 26, which is a rat MEKK1 active fragment.

32. The active fragment of claim 26, which consists of about amino acids 875-1493 of SEQ ID NO:4.

15 33. The active fragment of claim 26, which consists of about amino acids 685-1303 of SEQ ID NO:6.

34. An isolated protease-resistant MEKK1 protein comprising an amino acid sequence having at least 75% homology to the amino acid sequence of SEQ ID NO:4, wherein at least one amino acid equivalent to amino acids 871-874 of SEQ ID NO:4 is substituted such that the MEKK1 protein is resistant to proteolysis by a caspase after amino acid 874.

25 35. The MEKK1 protein of claim 34, wherein at least one amino acid equivalent to amino acids 871-874 of SEQ ID NO:4 is substituted with an alanine residue.

36. The MEKK1 protein of claim 34, wherein each amino acid equivalent to amino acids 871-874 of SEQ ID NO:4 is substituted with an alanine residue.

37. The MEKK1 protein of claim 34, which has at least 85% homology to the amino acid sequence of SEQ ID NO:4.

38. The MEKK1 protein of claim 34, which has at least 95% homology to the amino acid sequence of SEQ ID NO:4.

39. The MEKK1 protein of claim 34, which is a mouse MEKK1 protein.
40. The MEKK1 protein of claim 34, which is a human MEKK1 protein.
- 5 41. The MEKK protein of claim 40, consisting of amino acids 685-1303 of SEQ ID NO:6.
42. The MEKK1 protein of claim 34, which is a rat MEKK1 protein.
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- 10 43. An isolated nucleic acid molecule consisting of a nucleotide sequence having at least 75% homology to a nucleotide sequence consisting of about nucleotides 2637-4493 of SEQ ID NO:3, wherein said nucleic acid molecule encodes an active fragment of MEKK1 that mediates apoptosis.
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- 15 44. The nucleic acid molecule of claim 43, which consists of a nucleotide sequence having at least 85% homology to a nucleotide sequence consisting of about nucleotides 2637-4493 of SEQ ID NO:3.
45. The nucleic acid molecule of claim 43, which consists of a nucleotide
20 sequence having at least 95% homology to a nucleotide sequence consisting of about nucleotides 2637-4493 of SEQ ID NO:3.
46. The nucleic acid molecule of claim 43, which encodes an active fragment of a mouse MEKK1.
- 25 ^{P.126} 47. The nucleic acid molecule of claim 43, which encodes an active fragment of a human MEKK1.
48. The nucleic acid molecule of claim 43, which encodes an active fragment
30 of a rat MEKK1.
49. The nucleic acid molecule of claim 43, which consists of about nucleotides 2637-4493 of SEQ ID NO:3, or a nucleotide sequence that, due to the degeneracy of the genetic code, encodes the same amino acid sequence as about
35 nucleotides 2637-4493 of SEQ ID NO:3.

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50. The nucleic acid molecule of claim 43, which consists of nucleotides 2637-4493 of SEQ ID NO:3, or a nucleotide sequence that, due to the degeneracy of the genetic code, encodes the same amino acid sequence as nucleotides 2637-4493 of SEQ ID NO:3.

51. The nucleic acid molecule of claim 43, which consists of nucleotides 2052-3908 of SEQ ID NO:5, or a nucleotide sequence that, due to the degeneracy of the genetic code, encodes the same amino acid sequence as nucleotides 2052-3908 of SEQ ID NO:5.

52. An isolated nucleic acid molecule encoding a protease-resistant MEKK1 protein, wherein the protease resistant MEKK1 protein comprises an amino acid sequence having at least 75% homology to the amino acid sequence of SEQ ID NO:4 and at least one codon of the nucleic acid molecule encoding an amino acid equivalent to at least one of amino acids 871-874 of SEQ ID NO:4 is mutated such the encoded MEKK1 protein is resistant to proteolysis by a caspase after an amino acid equivalent to amino acid 871-874 of SEQ ID NO:4.

53. The nucleic acid molecule of claim 52, wherein the MEKK1 protein comprises an amino acid sequence having at least 85% homology to the amino acid sequence of SEQ ID NO:4.

54. The nucleic acid molecule of claim 52, wherein the MEKK1 protein comprises an amino acid sequence having at least 95% homology to the amino acid sequence of SEQ ID NO:4.

55. The nucleic acid molecule of claim 52, which encodes a protease-resistant mouse MEKK1 protein.

56. The nucleic acid molecule of claim 52, which encodes a protease-resistant human MEKK1 protein.

57. The nucleic acid molecule of claim 52, which encodes a protease-resistant rat MEKK1 protein.

58. An expression vector comprising the nucleic acid molecule of claim 43.

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59. An expression vector comprising the nucleic acid molecule of claim 52.

60. A host cell containing the expression vector of claim 58.

61. A host cell containing the expression vector of claim 59.

62. An isolated nucleic acid molecule encoding a protease-resistant MEKK1 protein, wherein the protease resistant MEKK1 protein comprises the amino acid sequence of SEQ ID NO:6 and at least one codon of the nucleic acid molecule encoding an amino acid equivalent to at least one of amino acids 681-684 of SEQ ID NO:6 is mutated such the encoded MEKK1 protein is resistant to proteolysis by a caspase after an amino acid equivalent to amino acid 681-684 of SEQ ID NO:6.

63. A method of stimulating apoptosis in a cell comprising introducing into the cell an expression vector encoding a MEKK1 active fragment such that MEKK1 active fragment is produced in the cell and apoptosis is stimulated.

64. A method of inhibiting apoptosis in a cell comprising introducing into the cell an expression vector encoding a protease-resistant MEKK1 protein such that protease-resistant MEKK1 protein is produced in the cell and apoptosis is inhibited.

65. A method of generating an MEKK1 active fragment *in vitro*, comprising: contacting an MEKK1 protein *in vitro* with a caspase protease under proteolysis conditions; and allowing the caspase protease to cleave the MEKK1 protein such that an MEKK1 active fragment is generated.

66. A method of identifying a compound that modulates the apoptotic activity of an MEKK1 active fragment, comprising: providing an indicator cell that comprises a MEKK1 active fragment; contacting the indicator cell with a test compound; and determining the effect of the test compound on the apoptotic activity of the MEKK1 active fragment in the indicator cell to thereby identify a compound that modulates the apoptotic activity of the MEKK1 active fragment.

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67. A method of identifying a compound that modulates the proteolytic cleavage of an MEKK1 protein by a caspase protease, comprising:

providing a reaction mixture that comprises an MEKK1 protein and a caspase protease;

- 5 contacting the reaction mixture with a test compound; and
determining the effect of the test compound on proteolytic cleavage of the
MEKK1 protein by the caspase protease to thereby identify a compound that modulates
the proteolytic cleavage of an MEKK1 protein by a caspase protease.

[illegible]